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THE CAUSE OF THE SECONDARY RISE
IN BLOOD PRESSURE FOLLOWING
PERIPHERAL SPLANCHNIC
NERVE STIMULATION

A DISSERTATION SUBMITTED TO THE
GRADUATE FACULTY IN CANDIDACY FOR
THE DEGREE OF DOCTOR OF PHILOSOPHY

DEPARTMENT OF PHYSIOLOGY

By
VICTOR EINAR JOHNSON

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VICTOR JOHNSON

From the Physiological Laboratories of the University of Chicago

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I. PREVIOUS WORK. Dreyer (1898) was the first observer to demonstrate that electrical stimulation of the peripheral end of the splanchnic nerve increases the output of adrenalin from the adrenal gland. In 1908 Lehdorff took blood pressure tracings while stimulating the peripheral splanchnics and obtained a curve consisting of a first and then a second rise. However, he did not mention adrenalin in the interpretation of his curves. Later Anrep (1912) stimulated these same nerves and observed an increase in the rate and tone of the denervated heart coincident with this secondary rise in blood pressure. When he clipped the adrenal veins there was no secondary rise and no cardiac change. He concluded then that "the secondary rise and all concomitant phenomena were due to the discharge of adrenalin into the circulation, and were absent after extirpation of the adrenal glands."

On the other hand Gley and his co-workers (1913, 1916, 1917, 1921, 1923) reported that in most dogs the secondary rise occurred even after double adrenalectomy. The same was found to be true of the cat, so that on the whole they were not in accord with the idea that the secondary rise was due to secreted adrenalin.

Pearlman and Vincent (1919) found on both cats and dogs that the blood pressure curve of splanchnic stimulation was seriously modified by elimination of the glands, although the total rise in pressure after adrenalectomy might even be greater than before. Their typical control curve consisted of a sharp primary rise with a step about half way up, then a "dip" followed by a secondary rise. After removing the glands they found the dip to be absent, so attributed its presence before adrenalectomy "to the discharge of adrenin in such doses as to produce a depressor effect."

Thus, while all workers are agreed that the primary rise is due to constriction of the splanchnic blood vessels from nervous activation of the vessel musculature, these contradictory interpretations of the secondary rise exist: 1, it is due entirely to pressor effects of adrenalin secreted by the adrenals; 2, it has no relation to the adrenal glands; 3, the dip between rises is due to the secretion of "depressor doses" of adrenalin.

II. PRESENT EXPERIMENTS. Because of this confusion about the cause of the secondary rise the present work was undertaken. Observations were made on sixty dogs under ether or barbital anesthesia. Through a midline incision the right splanchnic nerve was isolated and cut and the right adrenal gland removed. The left splanchnic was then isolated and cut and the peripheral end stimulated with either plain or shielded electrodes. Figure 1A is a tracing showing the effect on carotid blood pressure, of such a stimulation, the left adrenal still being intact. This kind of secondary rise coming just as the primary vaso-constriction has ceased we believe to be due mainly to the secretion of adrenalin by the adrenals because; 1, it is obtained in this form only when at least one adrenal is intact; 2, it is always modified (but not obliterated) by adrenalectomy or by occluding the lumbo-adrenal veins; 3, it is only with such a rise that dilatation of the sensitized pupil was seen.

After the second adrenal has been removed without injury to the splanchnics curves as in figures 1B and 1C were usually obtained. The curve is seen to consist of a sharp primary rise, a dip, and then a secondary rise with a subsequent drop to the pre-stimulation level. Frequently the secondary rise following the dip was higher than the primary rise.

Often even before the second adrenal was removed curves similar to those of figures 1B and 1C were obtained. This may probably be explained on the basis of the work of Elliott (1912), who showed that ether, chloroform, and other anesthetics exhausted the adrenalin supply of the glands if the splanchnics were intact. If then the adrenals are exhausted of adrenalin even before the control stimulation, the blood pressure curve before adrenalectomy would have the same appearance as after removal of the glands. Thus when Gley believed that adrenalectomy did not modify the blood pressure curve of splanchnic stimulation it may have been because he did not obtain the true adrenalin secondary rise before extirpation, simply because the anesthesia had depleted the adrenalin store of the gland. Furthermore Lehndorff's curves (1908) in his figures 2 and 6, both obtained before adrenalectomy, are almost identical with our curves in figures 1A and 1C respectively, the former taken before adrenalectomy, the latter, after. His curve of figure 6 is probably entirely independent of the adrenal glands although these were anatomically still intact.

Stimulation of either splanchnic after bilateral adrenal extirpation usually elicits similar curves, but occasionally one nerve fails to give a typical result. Rarely neither splanchnic gives the secondary rise, unless there has been undue trauma, or injury to the nerve, in which case the primary rise is also poor or even entirely lacking. The kind of anesthesia used is also a factor, for secondary rises were obtained more often when barbital was used.

III. POSSIBLE MECHANISMS INVOLVED. Concerning the cause of the

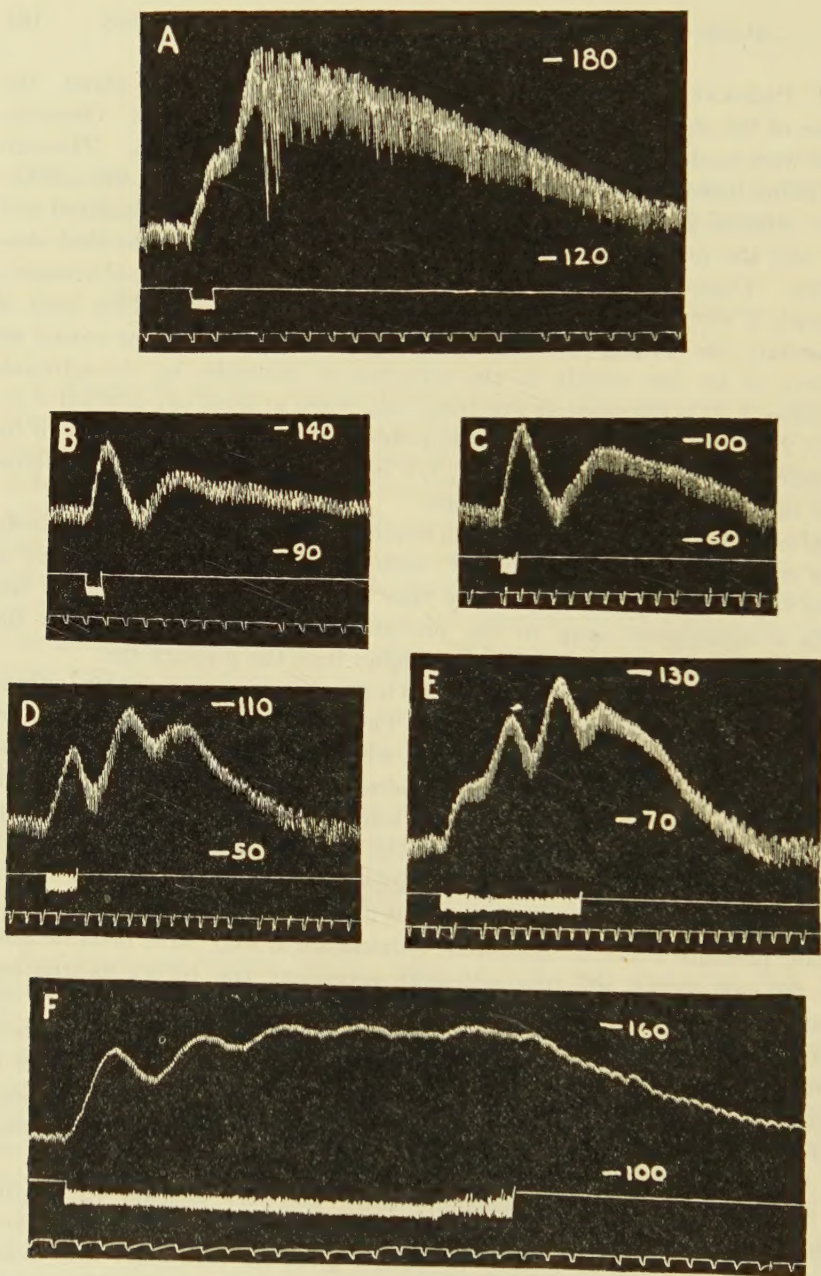


Fig. 1. Carotid blood pressure curves from peripheral splanchnic nerve faradization. Figures indicate millimeters of mercury. Signal marks application of stimulus. Time intervals are five seconds. A. Control. Right adrenal has been removed, left adrenal still intact. Stimulation of left splanchnic. B, C. Residual secondary rises after bilateral adrenalectomy. D, E, F. The same, except that several rises are seen.

residual secondary rise after bilateral adrenalectomy these mechanisms were considered. 1. *Reflexes*. Perhaps the elevated blood pressure of the primary rise might stimulate afferent nerves which would reflexly affect the heart or vaso-motor system in such a way as to bring about a second elevation. In adrenalectomized animals with double splanchnectomy, double vagotomy, or spinal cord section (at cervical 7) the secondary rise still persisted. Furthermore, this effect was observed immediately after cord section in the period of spinal shock, when presumably all reflexes are extremely poor or entirely abolished.

2. *Direct cardiac stimulation*. In addition to reflexes acting on the heart, changes in output might occur either through substances elaborated elsewhere than in the adrenals, or through changes in coronary pressure (Guthrie and Pike, 1907). The former possibility seemed to be excluded on the basis of experiments by Cannon (1922). The slight acceleration of the denervated heart which occurred on splanchnic stimulation after double adrenalectomy was practically abolished after section of the nerves

TABLE 1
Average heart rates accompanying changes in blood pressure following peripheral splanchnic stimulation in 12 adrenalectomized dogs

	HEART RATE DURING:					
	Control	Primary rise	Primary fall	Secondary rise	Secondary fall	Control
Average of 22 cases of stimulation...	127	134	128	137	119	121
Single stimulation in dog 32.....	86	55	154	84	87	90

to the liver. In our experiments the secondary rise in blood pressure after adrenalectomy was not abolished by so denervating the liver. In later work Cannon (1931) reports instances of cardiac acceleration from splanchnic stimulation even after adrenal extirpation and liver denervation.

However, the possibility of cardiac acceleration being a factor responsible for the secondary rise can be eliminated from the following considerations. The average heart rates during the different stages of the blood pressure curve in twenty-two instances of stimulation are shown in table 1. It must be borne in mind that these rates do not refer to denervated hearts and are thus not comparable to Cannon's data on the rate of the denervated heart. The question involved here is whether the intact heart increases its rate sufficiently to account for the secondary blood pressure rise.

In general it will be seen that the heart rate changes are in the same direction as the blood pressure variations. In six individual cases, however, there was an increase in rate with the primary fall, and a decrease

with the secondary rise. The heart rates in the most striking of these cases appear in line 2 of table 1. Furthermore, changes of rate of the order of magnitude indicated in line 1 of this table would probably be inadequate to account for the great changes in pressure sometimes observed. It is more likely that the increases in rate usually seen during the secondary rise are the result of the increased blood pressure and consequently improved coronary circulation, rather than the cause. For increases in rate equal to those of the secondary rise are also seen during the primary rise, which is admittedly a purely vaso-constrictor phenomenon.

The possibility must also be considered, of an increased stroke volume resulting from some change in the heart (e.g., increased coronary pressure) induced by the primary blood pressure elevation. Such an action would seem to be excluded on the basis of the fact that, although stimulation of either splanchnic elicited excellent and equal primary rises, presumably leading to equal changes in coronary pressure, yet only one splanchnic gave a secondary rise, in some animals.

3. *Peripheral mechanisms.* That this blood pressure curve was not due to any sort of rhythmic after-discharge either from the nerve at the point of stimulation, or from the coeliac ganglion, was shown in the following way: After cessation of stimulation, when the primary rise was at its height, the splanchnic nerve was cut about a half inch peripheral to the site of stimulation in such a way that the coeliac ganglion was also removed. This procedure had no effect on the curve.

We may conclude from all the above experiments that the secondary rise after adrenalectomy is due to the activity of some peripheral mechanism, some splanchnic nerve-end organ complex. The following of these were considered:

a. *Hepatic pressor substance.* It seemed reasonable to expect that the cardio-accelerator substance which Cannon (1922) demonstrated to be liberated from the liver on splanchnic stimulation is also a pressor substance. Elsewhere is mentioned the fact that denervation of the liver as described by Cannon resulted in no change in the blood pressure curve in the adrenalectomized animals.

b. *Splenic contraction.* With the idea of removing any blood pressure changes which might be induced by the contraction of the splenic smooth muscle, the spleen was temporarily cut out of the circulation after adrenalectomy. The splanchnics were then stimulated, and the typical curve with the double rise was again seen.

c. *"Adrenalin" from chromaffine tissue.* Could this secondary rise be due to the liberation of an adrenalin-like substance from the chromaffine bodies known to exist in the splanchnic region? If this were true, the presence of the material in the blood stream should produce effects on other

tissues than the blood vessel musculature. In 1904 Meltzer removed the superior cervical ganglion in rabbits and cats and after a few days found the pupil to be sensitive to adrenalin in amounts too small to affect the pupil of the normal eye. Elliott (1912) found that in doubly adrenalectomized cats with one superior cervical ganglion removed, stimulation of the splanchnics led to slight pupillary dilatation in a few cases. He suggested that this might result from adrenalin liberated by the paraganglia or by the actual processes of nervous excitation, or from other metabolites. Hartman (1923), using the supersensitive eyes of cats, reports little or no response on stimulation of the splanchnics after adrenalectomy. Stewart and Rogoff, however (1916), in the same experiment on dogs, found that the response of the partially denervated eye was due solely to adrenal adrenalin, and was absent when the venous path from the glands was blocked. Our results on dogs confirm those of Stewart and Rogoff. The discrepancy between the positive and the negative results of these investigators, may possibly be explained on the basis of species differences. Perhaps the pupil of the cat's eye is more sensitive to adrenalin-like substances than that of the dog. Or perhaps splanchnic stimulation leads to the liberation of more such material in the cat than in the dog. At any rate, the negative experiments do not preclude the possibility of a pressor, adrenalin-like substance being responsible for the secondary rises.

Nor does the fact that the secondary rises in figures 1B and 1C (after adrenalectomy) appear later than in figure 1A (control) negate the possibility of such a mechanism. This longer latent period might merely mean that the substance is not as readily available for secretion as is adrenalin from the adrenals, and the beginning of the response, therefore, is delayed.

The secondary rise may be another manifestation of the phenomenon described by Cannon (1931) in which he concludes that smooth muscle under sympathetic control may be made to liberate a substance with an adrenalin-like action when its motor nerve is stimulated.

d. Peripheral vascular rhythm. Might not the residual secondary rise be a manifestation of a rhythmical vascular response to stimulation? For in some cases there are observed not only two rises, but three (fig. 1D) or even more (figs. 1E and 1F), especially if the stimulation is prolonged. When Carlson (1907) stimulated the cervical sympathetic in the cat, which carries a predominance of vaso-dilator fibers, he observed occasionally a rhythmical variation in the blood flow from the submaxillary gland. This observation would also be in accord with the idea that blood vessel musculature responds to nervous stimulation by rhythmical variations in tone. The heart is a modified blood vessel, and it is not inconceivable that its characteristic property of rhythmical activity is possessed by blood vessels in general.

IV. CONCLUSIONS

1. The secondary rise in blood pressure on peripheral splanchnic stimulation is partly due to the secretion of adrenalin from the adrenals, and partly due to some other factor, for it is seen in modified form after double adrenalectomy.

2. The residual secondary rise is not due to reflexes, contraction of the spleen, or liberation of a pressor or cardio-accelerator substance from the liver, and is probably not due to increased cardiac output. Nor is it the result of any sort of intermittent after-discharge from the stimulated region of nerve, or from the coeliac ganglion.

3. It is believed to be a peripheral phenomenon involving a splanchnic nerve-end organ mechanism. This end organ may be chromaffine tissue liberating an adrenalin-like substance, or some other tissue possibly the blood vessel musculature, elaborating a pressor substance (i.e., Cannon's "sympathin"). Or it may be rhythmically contracting vascular musculature.

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